More than Skin Deep! – Chronic Spontaneous Urticaria and Hereditary Angioedema

Dr Jeanette Holtzhausen

University of Cape Town Lung Institute

Allergy diagnostic and Clinical Research Unit and Lung Clinical Research Unit

www.lunginstitute.co.za

MBChB. B.Sc. Hons (Pharmacology) DCH Dip Allergology

Jeanette.holtzhausen@uct.ac.za

Declaration of Conflict of Interest

- No conflict of interest to declare
- Clinical research physician and limited private practice, UCT Lung Institute, Cape Town, South Africa

Overview

- Define urticaria and angioedema
- Basic approach to ‘itching and swelling’
- Investigation and treatment of Chronic Spontaneous Urticaria
- Illustrative urticaria cases
- Discuss angioedema, in particular hereditary angioedema

www.geology.uct.ac.za/cape/town/geology

Who is this lady in the painting?

Public Domain, https://commons.wikimedia.org/w/index.php?curid=1372096

An example of a drawing, of "Paradise", her South African residence

Where was this picture taken and what do you have to look out for in this area?

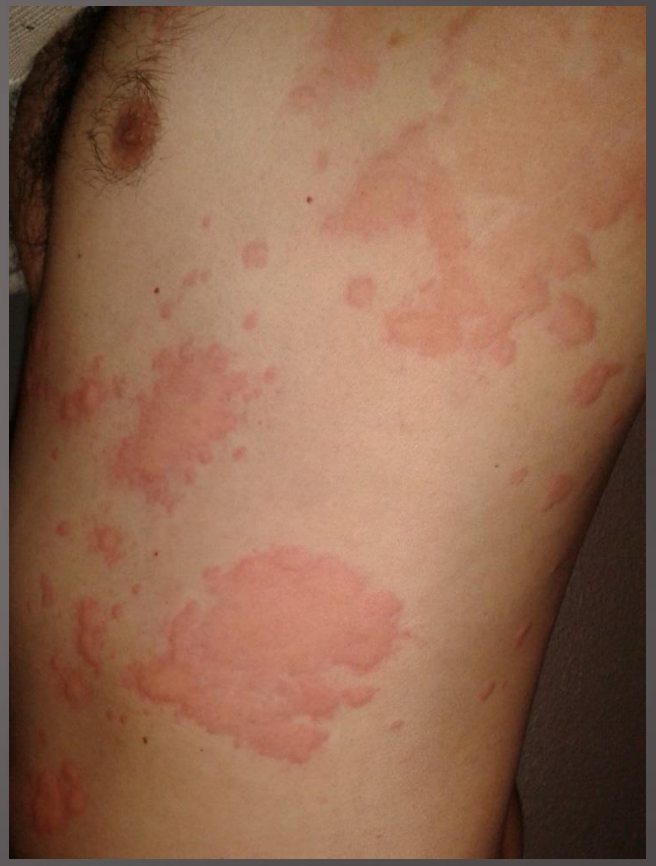
Kirstenbosch National Botanical Gardens

Urticaria named after *Urticaeceae* species of stinging nettle plants

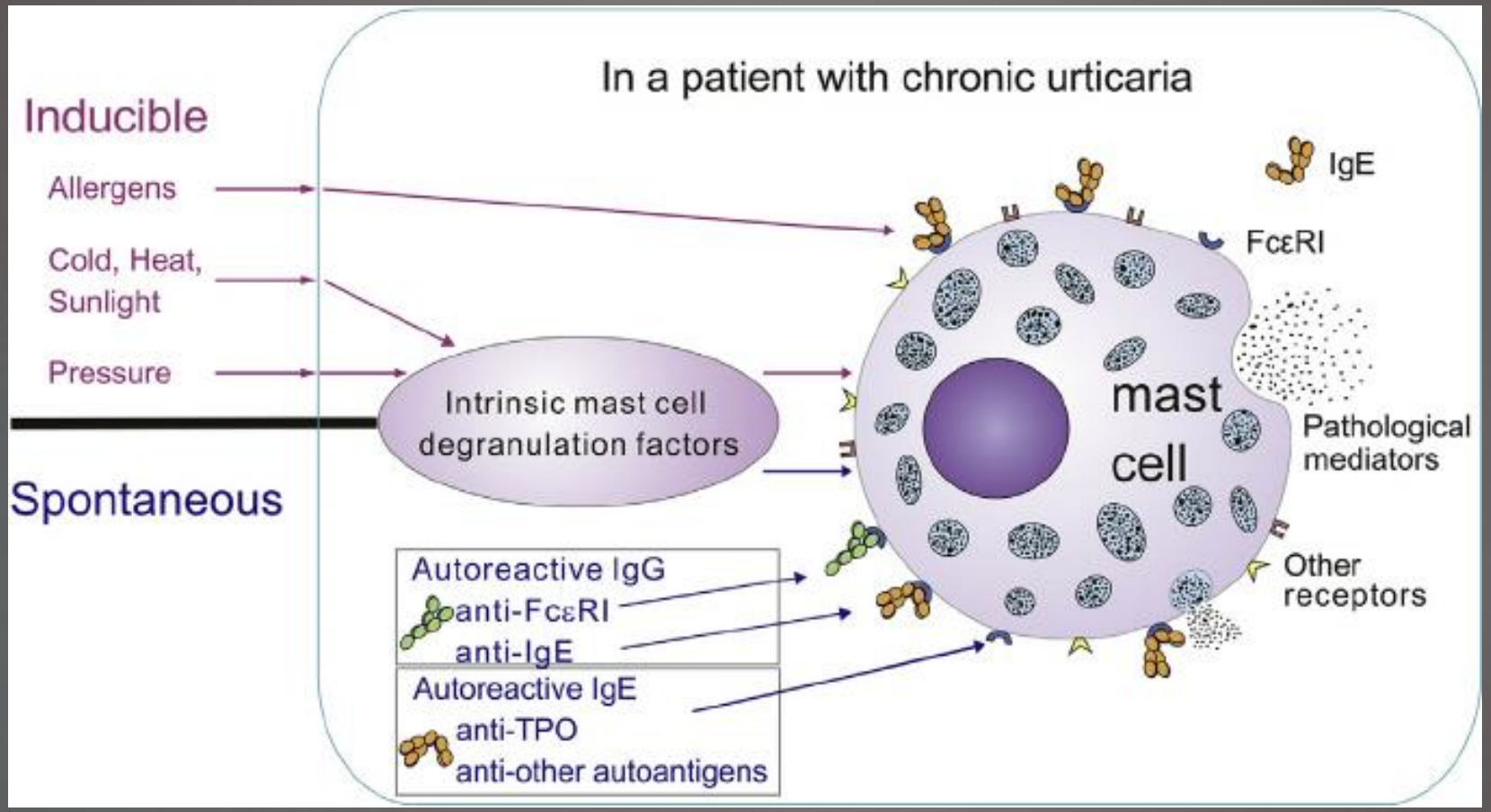
The Latin root of the word urticaria is *urere*, meaning – 'to burn', as is evident in the family name of the *Urticaceae* stinging nettle plants. The classic 'wheal and flare' histamine response is illustrated by the discomfort experienced upon cutaneous contact with these plants!

Urticaria – clinical features

- Polymorphic, raised and erythematous lesions
- Vasodilatation
- Increased vascular permeability
- Following release of mediators by mast cells
- Individual lesions resolve within 24 hours
- No scarring – epidermis not involved
- Intensely pruritic
- Rash tends to ‘migrate’ or become confluent.



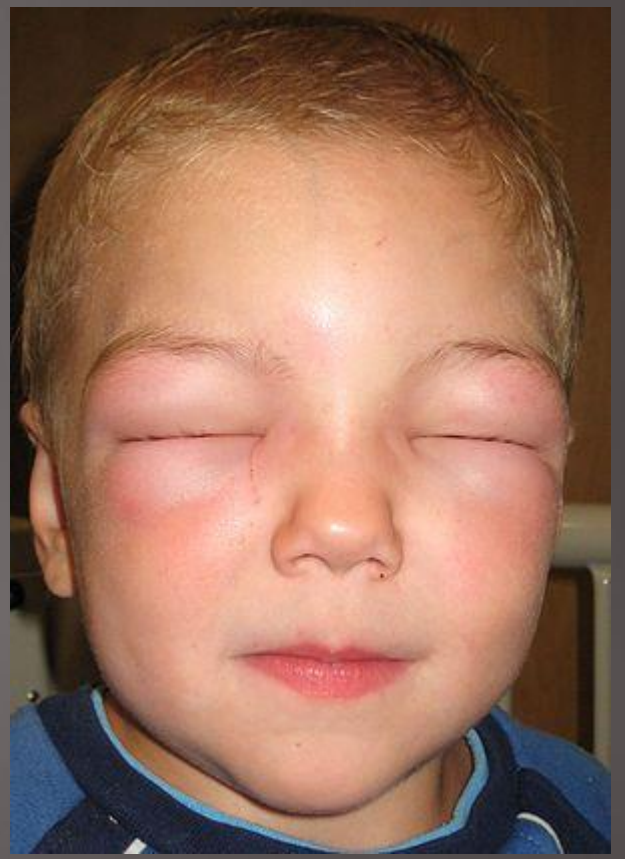
Mast cell degranulation in urticaria



https://www.researchgate.net/figure/263292170_fig1_FIG-1-The-inflammatory-manifestation-of-mast-cells-in-affected-skin

Angioedema

- Swelling of deep dermis, subcutaneous or mucocutaneous tissue
- Due to vascular leakage
- Face, eyelids and lips commonly affected
- May affect limbs, gastro intestinal system, airway
- Painful lesions, rather than pruritic
- Take up to 72 hours to resolve
- Can be histamine mediated or through the complement/bradykinin pathway

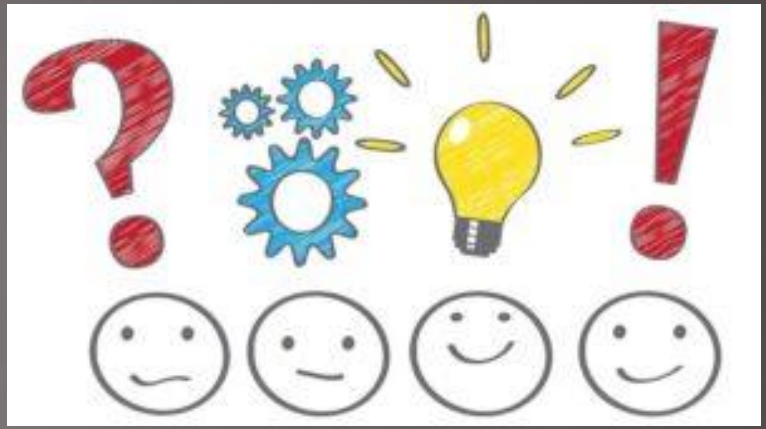


Picture - https://en.wikipedia.org/wiki/Angioedema

Where to Start - History is MOST IMPORTANT!

EAACI/GA2LEN/EDF/WAO 2013 urticaria guideline - recommended key questions

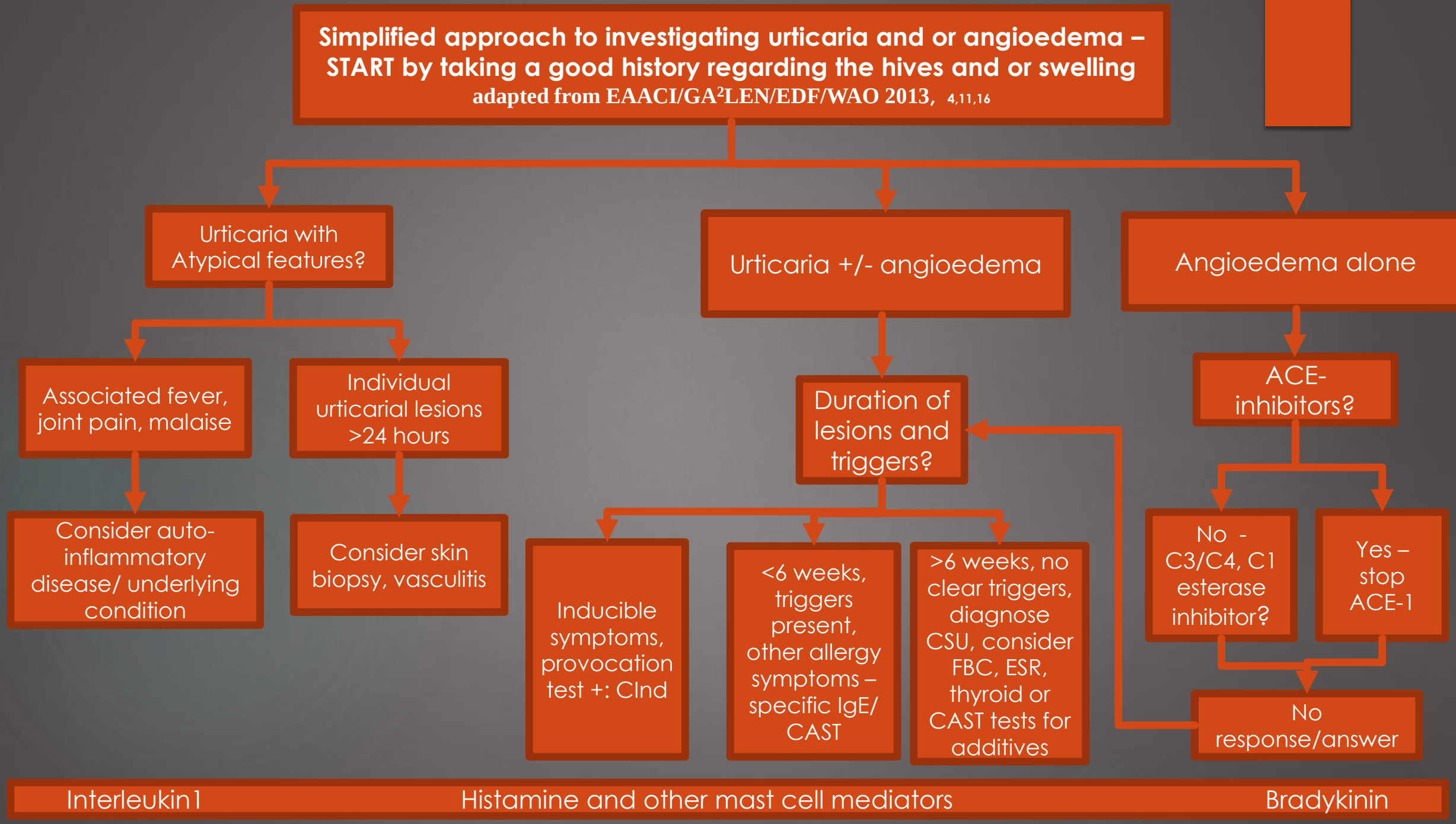
1. Time of onset of disease
2. Frequency/duration of and provoking factors for hives
3. Diurnal variation
4. Occurrence in relation to weekends, holidays, and foreign travel
5. Shape, size, and distribution of hives
6. Associated angioedema
7. Associated subjective symptoms of lesions, for example itch, pain
8. Family and personal history regarding urticarial/atopy
9. Previous or current allergies, infections, internal diseases, or other possible causes
10. Psychosomatic and psychiatric diseases
11. Surgical implantations and events during surgery, for example after local anesthesia
12. Gastric/intestinal problems
13. Induction by physical agents or exercise
14. Use of drugs (e.g., non-steroidal anti-inflammatory drugs (NSAIDs), injections, immunizations, hormones, laxatives, suppositories, ear and eye drops, and alternative remedies)
15. Observed correlation to food
16. Relationship to the menstrual cycle
17. Smoking habits (especially use of perfumed tobacco products or cannabis)
18. Type of work
19. Hobbies
20. Stress (eustress and distress)
21. Quality of life related to urticaria and emotional impact
22. Previous therapy and response to therapy
23. Previous diagnostic procedures/results



EAACI, European Academy for Allergy and Clinical Immunology; EDF, European Dermatology Forum; GA2LEN, Global Allergy and Asthma European Network; WAO, World Allergy Organization.
Reproduced from Zuberbier et al. Allergy 2014;69(7):868–87.

Patient presents with ‘itching and swelling’ – Key questions

- Is it urticaria? (Consider alternative dermatological diagnosis…24 hours, epidermis involvement, vasculitis…)
- Does the patient present with urticaria, angioedema or both?
- Duration (6 weeks – Acute or chronic)
- Is there atopy, allergy, anaphylaxis on history
- What are the triggers IN THIS CASE
- Physical factors, foods, medicines or additives, stress, underlying medical conditions?
- Does it respond to antihistamines or not, QOL?


Simplified approach to investigating urticaria and or angioedema – START by taking a good history regarding the hives and or swelling
adapted from EAACI/GA²LEN/EDF/WAO 2013, 4,11,16
Urticaria with Atypical features?
Urticaria +/- angioedema
Angioedema alone
Associated fever, joint pain, malaise
Individual urticarial lesions >24 hours
Consider auto-inflammatory disease/ underlying condition
Consider skin biopsy, vasculitis
Duration of lesions and triggers?
Inducible symptoms, provocation test +: CInd
<6 weeks, triggers present, other allergy symptoms – specific IgE/ CAST
>6 weeks, no clear triggers, diagnose CSU, consider FBC, ESR, thyroid or CAST tests for additives
ACE-inhibitors?
No - C3/C4, C1 esterase inhibitor?
Yes – stop ACE-1
No response/answer
Interleukin1
Histamine and other mast cell mediators
Bradykinin

Chronic spontaneous urticaria

- Daily/ frequent occurrence
- Pruritic Hives and/ or Angioedema
- > 6 weeks
- Distinguished from inducible types
- Synonym Chronic Idiopathic Urticaria
- **“Easy to diagnose, difficult to treat”**

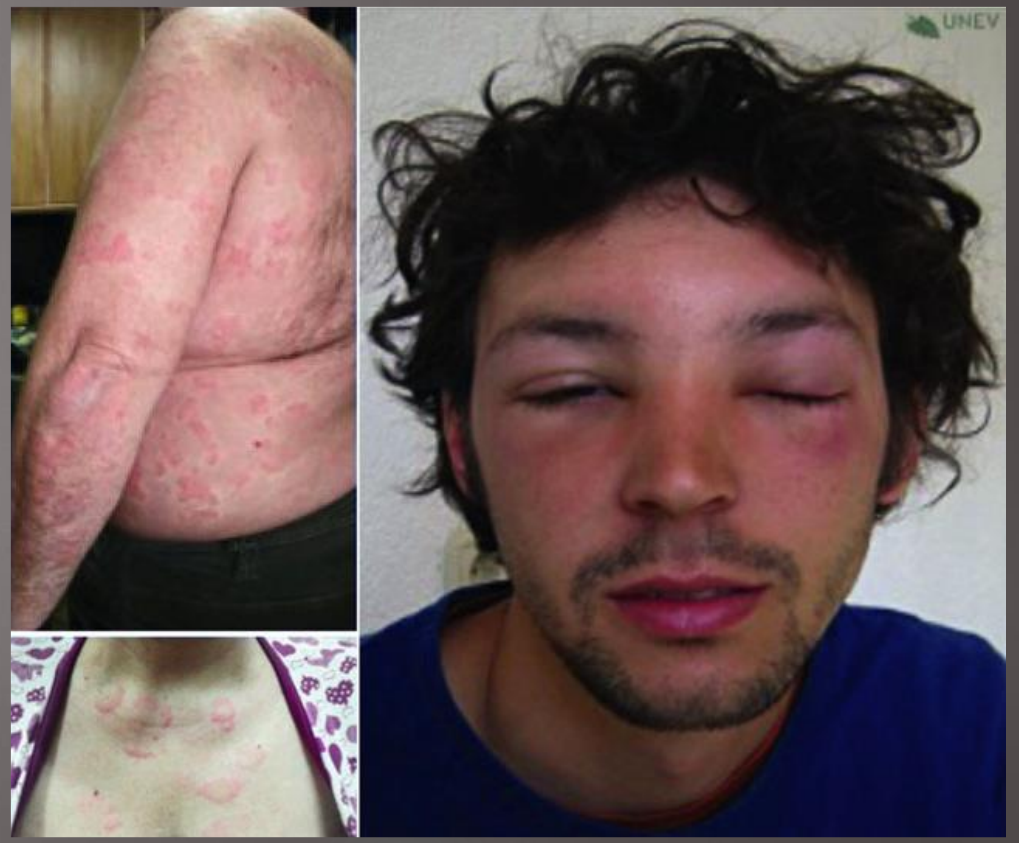


Figure 1 Symptoms of urticaria.
(a**) Hives** – central swellings of variable size, often surrounded by reflex **erythema**. Associated with itching; individual hives usually resolve within 1–24 h;
(b) **Angioedema** – sudden, pronounced erythematous or skin coloured swelling of the lower dermis and subcutis with frequent involvement below mucous membranes. Sometimes associated with pain rather than itching; resolution can take up to 72 h.
Photographs (a) courtesy of Novartis Pharma AG; (b) reproduced with kind permission from UNEV; patient consent received.
Published in JEADV 2016 (Suppl 5), 9

Diagnostic tests for Chronic Spontaneous Urticaria EAACI/GA2LEN/EDF/WAO 2013

Routine	Extended
Differential blood count	Infectious diseases
ESR/CRP	Type 1 allergy (IgE)
Omission of suspected drugs	Auto-antibodies
	Thyroid hormones
	Skin tests
	Pseudoallergens
	Serum tryptase
	ASST (autologous serum skin test)
	Skin biopsy (vasculitis)

Extended tests not routinely recommended
– choice based on clinical evaluation (PERSONAL AND FAMILY HISTORY NB)

CSU – Current treatment guidelines

(EAACI/GA²LEN/ EDF/ WAO 2013)

- 1. First line – Modern second generation antihistamines

If symptoms persist after 2 weeks

- 2. Second line – Increase dosage to 4 fold of modern second generation antihistamines

If symptoms persist after a further 1 to 4 weeks

- 3. Third line – Add to second line Omalizumab or Ciclosporin A or Montelukast

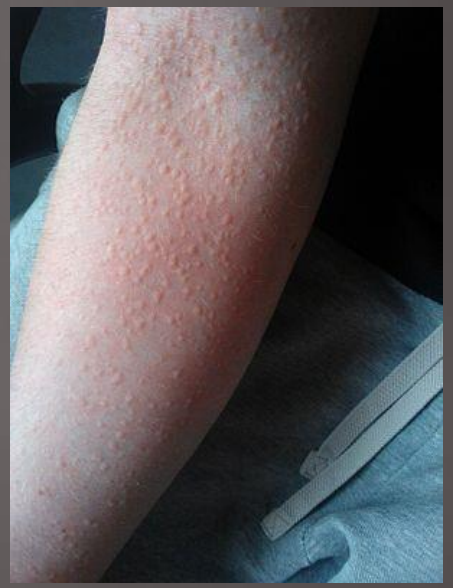
* Short course steroids <10 days used at any time for exacerbations

Case 1 – Mr. Nick de Kick

- Rugby player with high aspirations
- History of seasonal allergic rhinitis
- Now pruritic skin rashes
- Triggers – sweat and exercise
- Contact with grass
- ‘Strapping’ plasters

Case 1 - Mr. Nick de Kick

- Features of allergic rhinitis
- Dermatographism
- Fine cholinergic urticaria
- Also – T cell mediated contact dermatitis reaction in distribution where strapping had been applied
- How would you investigate him?



https://en.wikipedia.org/wiki/Cholinergic_urticaria

Case 1 Mr. Nick de Kick

- No angioedema
- Typical cholinergic urticaria, individual lesions resolve in less than 24 hours
- >6 weeks, but recently exacerbated since training intensified
- Features of atopy, clear triggers (grass, exercise), no anaphylaxis
- Co-morbid contact dermatitis to plaster glue, allergic rhinitis
- Partial response to OTC antihistamines

Mr. Nick de Kick

Simplified approach to investigating urticaria and or angioedema – START by taking a good history regarding the hives and or swelling

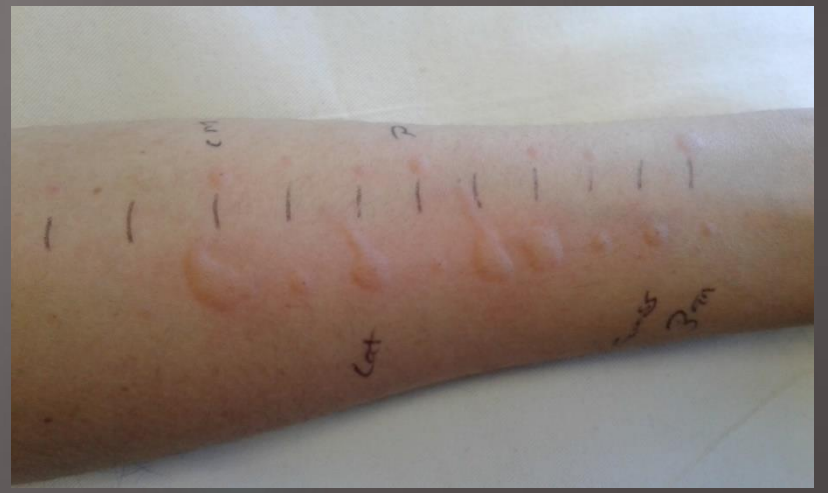
adapted from EAACI/GA²LEN/EDF/WAO 2013, [4,11,16]

- Urticaria with Atypical features?
  - Associated fever, joint pain, malaise → Consider auto-inflammatory disease/ underlying condition
  - Individual urticarial lesions >24 hours → Consider skin biopsy, vasculitis
- Urticaria +/- angioedema → Duration of lesions and triggers?
  - Inducible symptoms, provocation test +: CInd
  - <6 weeks, triggers present, **other allergy symptoms – specific IgE/ CAST**
  - >6 weeks, no clear triggers, diagnose CSU, consider FBC, ESR, thyroid or CAST tests for additives
- Angioedema alone → ACE-inhibitors?
  - No - C3/C4, C1 esterase inhibitor?
  - Yes – stop ACE-1
  - No response/answer → Duration of lesions and triggers?

Interleukin1 | Histamine and other mast cell mediators | Bradykinin

Case 1 Mr. Nick de Kick - Management

- Skin prick testing confirmed IgE mediated allergy to grass pollen
- MIXED PICTURE – grass pollen allergy, cholinergic urticaria, T cell mediated skin reactions to strapping
- Intranasal steroid and rupatidine prescribed
- Urticaria completely controlled at follow up
- Advised to try hypo-allergenic strapping
- Consider patch testing
- Consider grass pollen SLIT



Case 2 - Ms. Numara Sleep

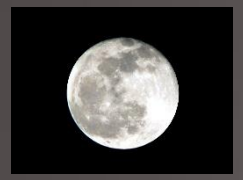
- 31 year old female
- 5 months postpartum – breastfeeding
- Urticaria and angioedema 'off and on' in the past, but severe since birth of baby – distressed
- Physical examination unremarkable, mild 'sinus'
- General practitioner hesitant to prescribe antihistamines
- Multiple ER visits – needed parenteral steroids, antihistamines – CAN WE HELP THIS LADY?

http://www.publicdomainpictures.net/view-image.php?image=17108&picture=breastfeeding&large=1

Case 2 - Ms. Numara Sleep

- Typical urticarial wheals
- Angioedema also present
- Longstanding - > 6 weeks – chronic by definition
- Unsure about atopy status…
- Triggers… immune modulatory effect of pregnancy, stress and sleep deprivation
- Family history – mother has hypothyroidism

Ms. Numara Sleep



Simplified approach to investigating urticaria and or angioedema – START by taking a good history regarding the hives and or swelling

adapted from EAACI/GA²LEN/EDF/WAO 2013, [4,11,16]

- Urticaria with Atypical features?
  - Associated fever, joint pain, malaise → Consider auto-inflammatory disease/ underlying condition
  - Individual urticarial lesions >24 hours → Consider skin biopsy, vasculitis
- Urticaria +/- angioedema → Duration of lesions and triggers?
  - Inducible symptoms, provocation test +: CInd
  - <6 weeks, triggers present, other allergy symptoms – specific IgE/ CAST
  - **>6 weeks, no clear triggers, diagnose CSU, consider FBC, ESR, thyroid or CAST tests for additives**
- Angioedema alone → ACE-inhibitors?
  - No - C3/C4, C1 esterase inhibitor?
  - Yes – stop ACE-1
  - No response/answer → Duration of lesions and triggers?

Interleukin1 | Histamine and other mast cell mediators | Bradykinin

Case 2 – Ms. Numara Sleep

- Skin prick tests negative to inhalant allergens (history of 'sinus' - viral infections)
- Ordered FBC - Normal, ESR =14 mm/hr.
- CAST's declined – cost and 'clean diet'
- Thyroid function and auto-antibody investigations
- Results - Free T4 10.6 (7.2 – 16.4 pmol/L)
  TSH 8.12 H (0.38 – 5.33 mIU/

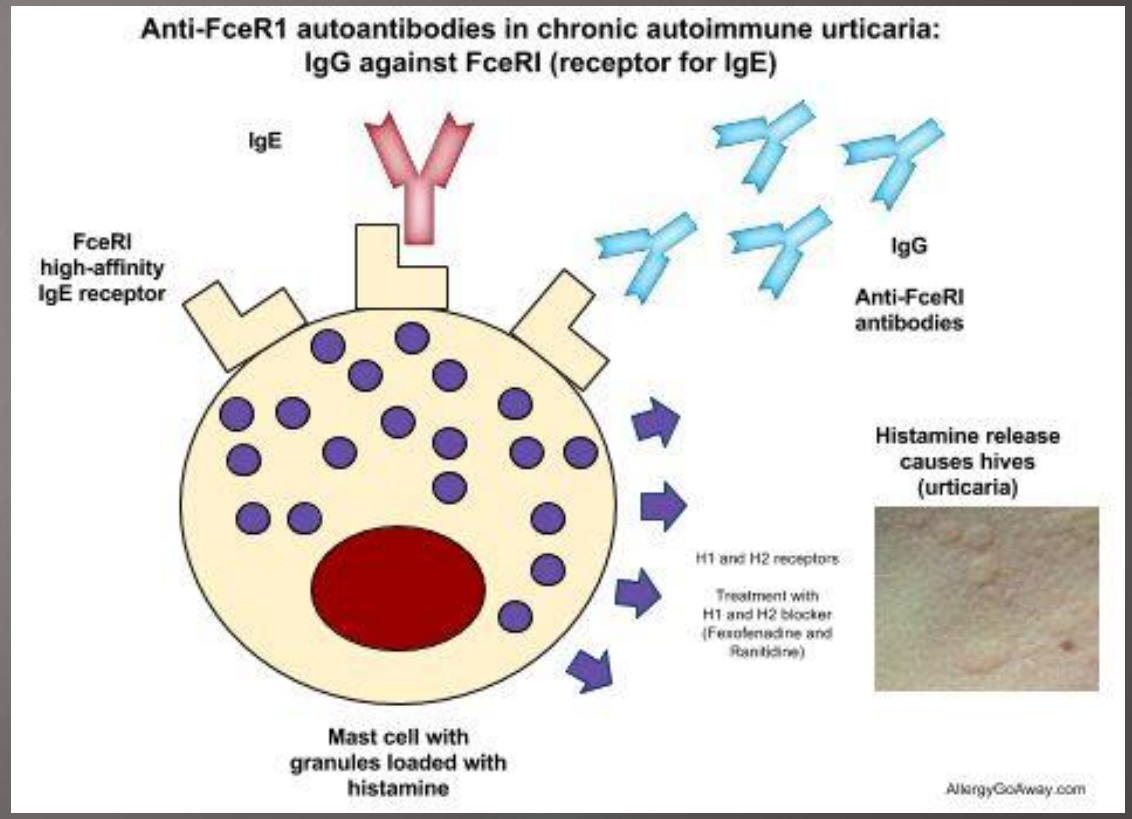
Subclinical hypothyroidism

Case 2 – Ms. Numara Sleep

THYROGLOBULIN AB 46.6 H (0-4.0 IU/mL)

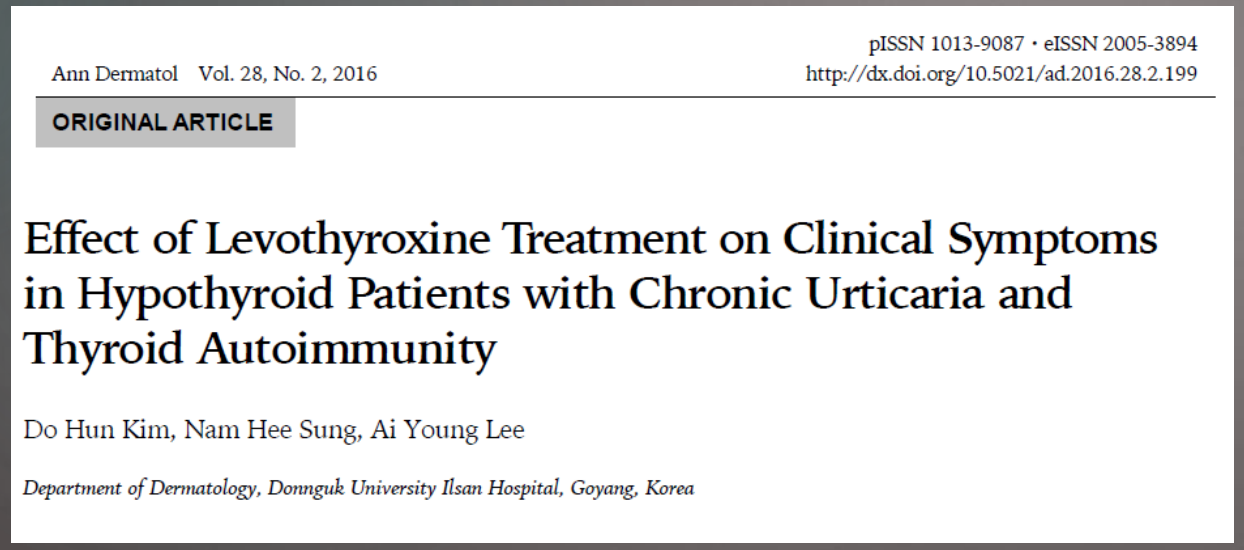
Thyroid Peroxidase Ab >1068.0 H (0-9 Iu/mL)

- Clinical significance?
- **Possible auto-immune mechanism for CSU - thyroid auto-antibodies interacting with the mast cells?**
- Managed as CSU – Cetirizine/ Levocetirizine
- Reassured that continued breastfeeding while weaning acceptable despite antihistamines
- **Follow up of thyroid functions, possible endocrinology referral**
- Omalizumab potential future option for her



Association between CSU and thyroid auto-immunity

- Anti-thyroid peroxidase, Anti-thyroglobulin antibodies
- Patients with +ASST more likely to have thyroid disease/ antibodies (Lunge et al)
- CSU associated with thyroid disease/ auto-immunity often severe



pISSN 1013-9087 · eISSN 2005-3894
Ann Dermatol Vol. 28, No. 2, 2016 http://dx.doi.org/10.5021/ad.2016.28.2.199

ORIGINAL ARTICLE

Effect of Levothyroxine Treatment on Clinical Symptoms in Hypothyroid Patients with Chronic Urticaria and Thyroid Autoimmunity

Do Hun Kim, Nam Hee Sung, Ai Young Lee

Department of Dermatology, Donnguk University Ilsan Hospital, Goyang, Korea

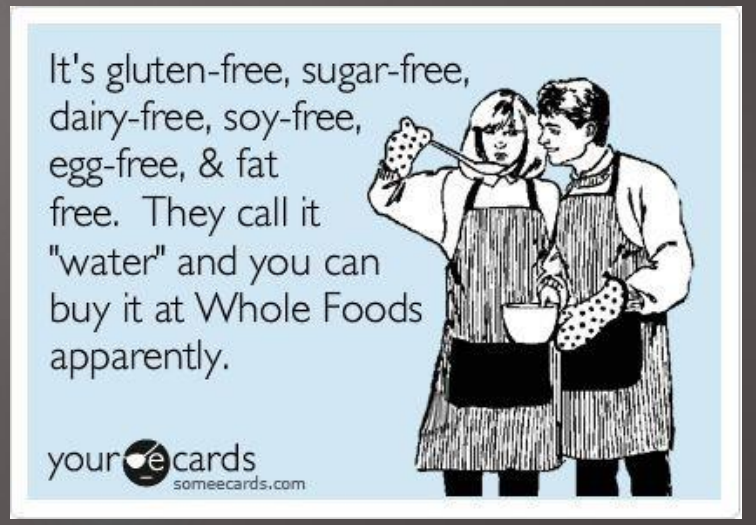
KIM et al, Korea 2016:
184 patients with CSU
43 (23 %) -anti thyroid antibodies
26 (14 %) -thyroid dysfunction (Hyper and hypothyroidism)
Only 2 patient's urticaria improved after Rx of thyroid condition

Case 3 – Ms. Truly Desperate

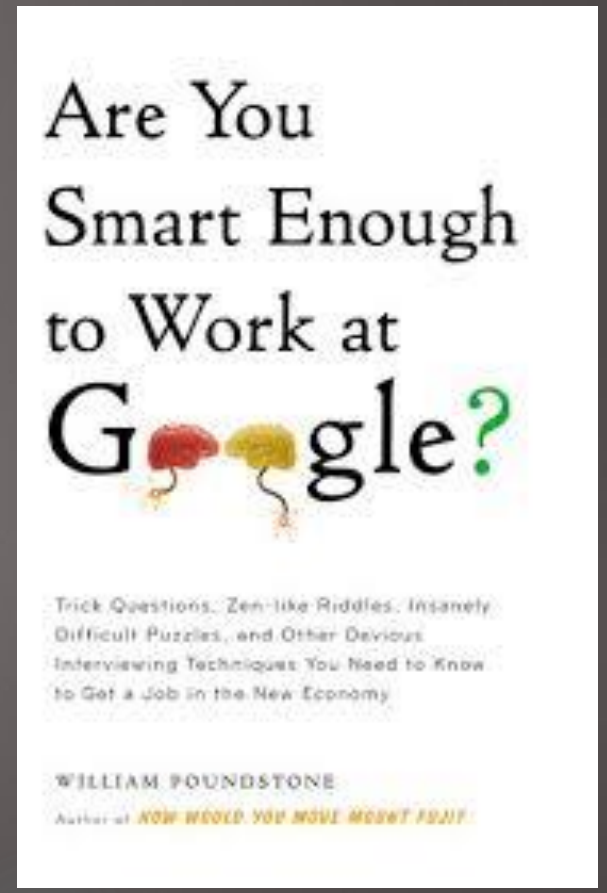
- 42 year old marketing manager
- Background of well controlled asthma and rhinitis
- However – allergic to her 5 cats!
- 18 months history of severe urticaria
- No angioedema
- Mom has rheumatoid arthritis

Case -3 Ms. Truly Desperate

- Avoiding gluten, diary and sugar – multiple 'triggers'
- On omega 3 and probiotics ex naturopath
- Longstanding depression well controlled on citalopram
- Oral contraceptive tablet
- On fexofenadine 180 mg am, Phenergan 25 mg pm
- Relying on Celestamine and steroid injections
- 'It's the only thing that helps'!



Who wants to suggest a plan?



Ms. Truly Desperate

- Challenging case and personality!
- Definitely atopic
- Longstanding disease – chronic, urticaria without angioedema
- Confusing detailed list of triggers – palm oil to tight clothing
- Psychological factors and stress likely to be contributory
- Seemingly unresponsive to antihistamines
- Steroid dependent

Ms. Truly Desperate

Simplified approach to investigating urticaria and or angioedema – START by taking a good history regarding the hives and or swelling

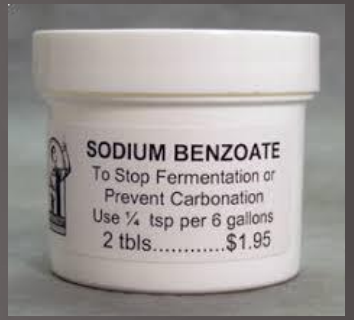
adapted from EAACI/GA²LEN/EDF/WAO 2013, [4,11,16]

- Urticaria with Atypical features?
  - Associated fever, joint pain, malaise → Consider auto-inflammatory disease/ underlying condition
  - Individual urticarial lesions >24 hours → Consider skin biopsy, vasculitis
- Urticaria +/- angioedema → Duration of lesions and triggers?
  - Inducible symptoms, provocation test +: CInd
  - <6 weeks, triggers present, other allergy symptoms – specific IgE/ CAST
  - **>6 weeks, no clear triggers, diagnose CSU, consider FBC, ESR, thyroid or CAST tests for additives**
- Angioedema alone → ACE-inhibitors?
  - No - C3/C4, C1 esterase inhibitor?
  - Yes – stop ACE-1
  - No response/answer → Duration of lesions and triggers?

Interleukin1 | Histamine and other mast cell mediators | Bradykinin

Case 3 Ms. Truly Desperate: Investigations

- Normal physical exam and acceptable lung functions
- + Dermatographism
- SPT positive cats, dogs, grass and birds
- CASTs moderately reactive to benzoates
- Normal FBC, ESR, CRP
- Negative rheumatoid factor and auto-immune screen
- Normal thyroid function and negative thyroid auto-antibodies



Case 3 Ms. Truly Desperate - Management

- No response to increasing doses, various chemical classes of antihistamines
- Eliminating alcohol and benzoates helped, but still had severe distressing symptoms
- Self imposed dietary restrictions affecting QOL
- Ongoing reliance on oral steroids – weight gain, Cushingoid appearance and adrenal suppression a real concern
- No response to omalizumab
- Patient resigned from stressful job – thereafter slowly weaned off steroids.

Omalizumab in CSU

- Glycosylated IgG monoclonal antibody produced by cells of an adapted Chinese hamster ovary (CHO) cell line.
- Licensed for severe allergic asthma
- Since 2014 in patients >12 with CSU
- Binds to free IgE
- Mast cell downregulates high affinity IgE receptors…
- Anaphylaxis risk – administration in hospital setting
- Effective in 75 % of patients, but COST is an issue

Psychological factors in urticaria

- Condition may start / flare up during times of "stress" (bereavement, overseas travel, business meetings, wedding and honeymoon!)
- Urticaria also causes psychological distress due to intense pruritus and embarrassing appearance
- Severe impact on quality of life – functional and sleep impairment common
- Not to be trivialised – offer emotional support

Urticaria - conclusions

- Mast cells, histamine mediated
- Distinguish acute vs chronic urticaria (6 weeks)
- History important to determine investigations – use algorithm and guidelines (NO reflex ticking of boxes!)
- Chronic spontaneous urticaria NOT usually IgE mediated
- Variable triggers (e.g. physical factors, food additives, auto-immune or underlying conditions, stress)

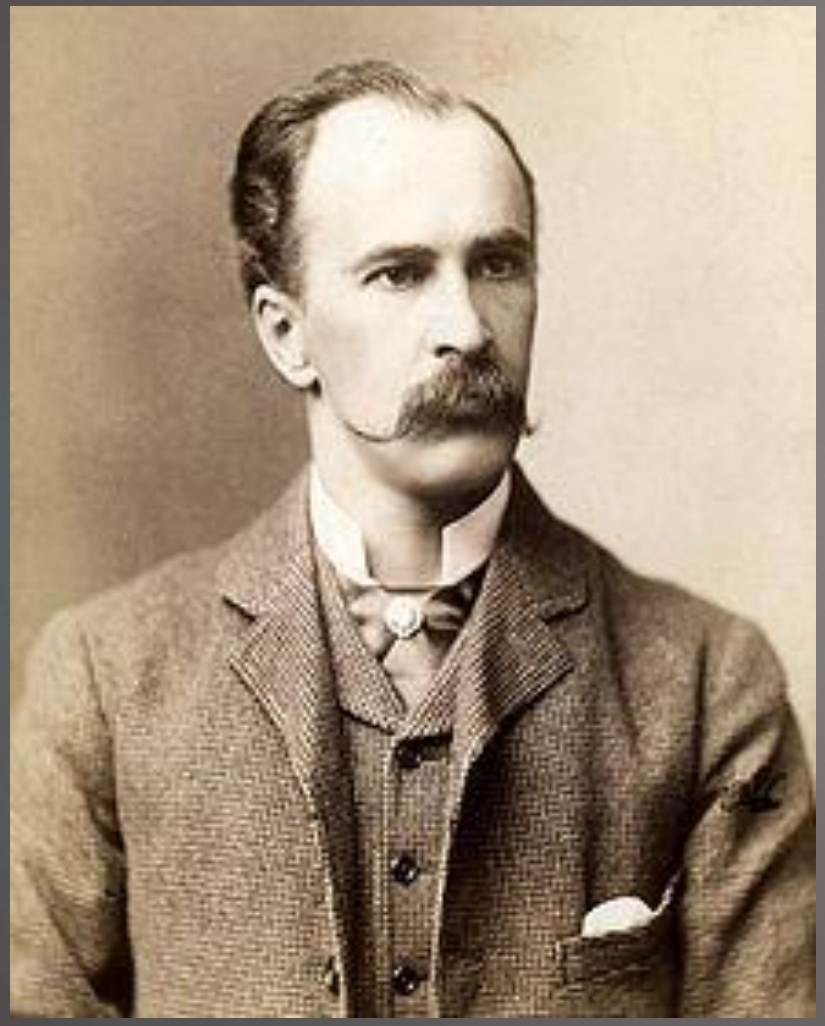
Majority can be managed by high dose non-sedating antihistamines

Avoid excessive oral steroids – short courses only

Omalizumab may be a game changer in severe cases

Chronic urticaria consultation – common scenario!

Who was this famous doctor? What is the relevance to our topic?



"Listen to your patient, he is telling you the diagnosis"

"Medicine is a science of uncertainty and an art of probability."

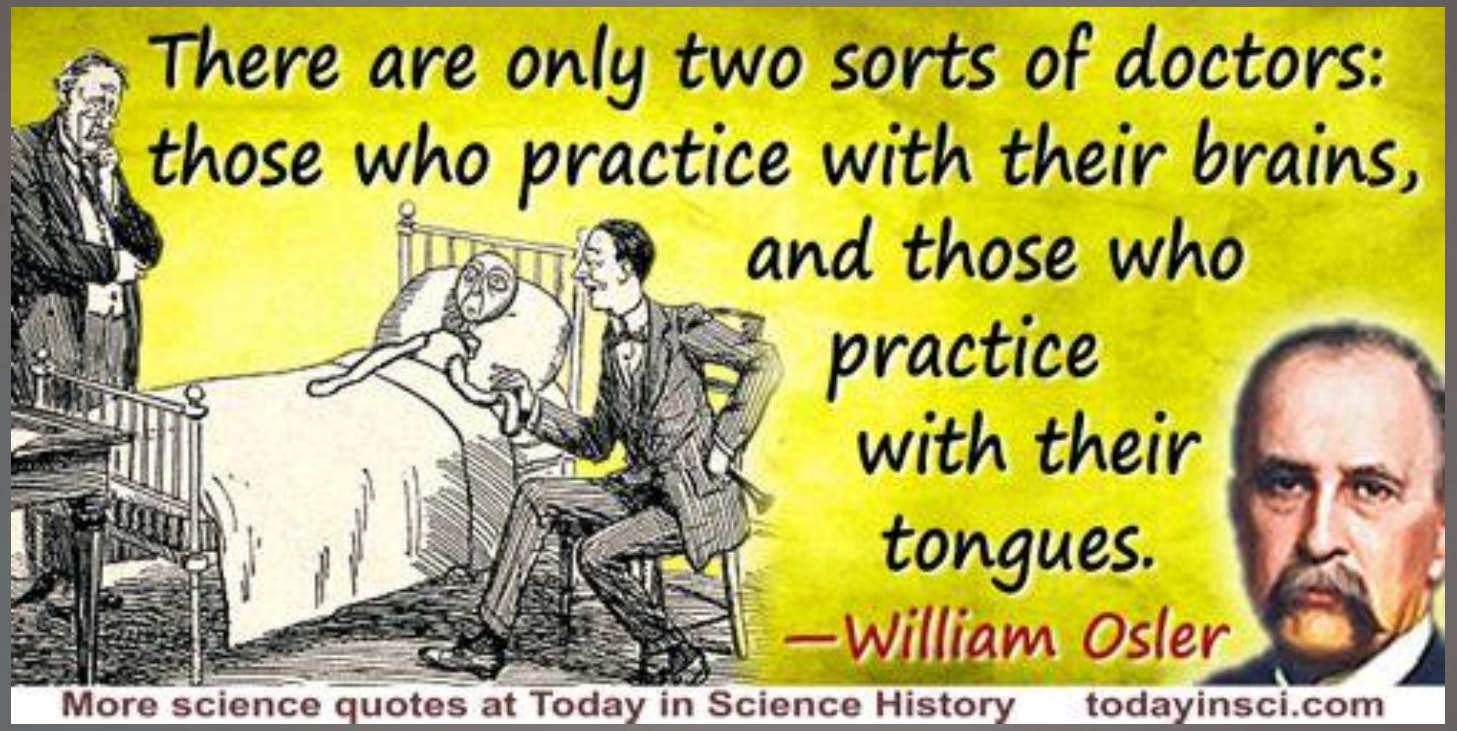
"It is much more important to know what sort of patient has a disease, than what disease a patient has."

He has frequently been described as the "Father of Modern Medicine" and one of the "greatest diagnosticians ever to wield a stethoscope"

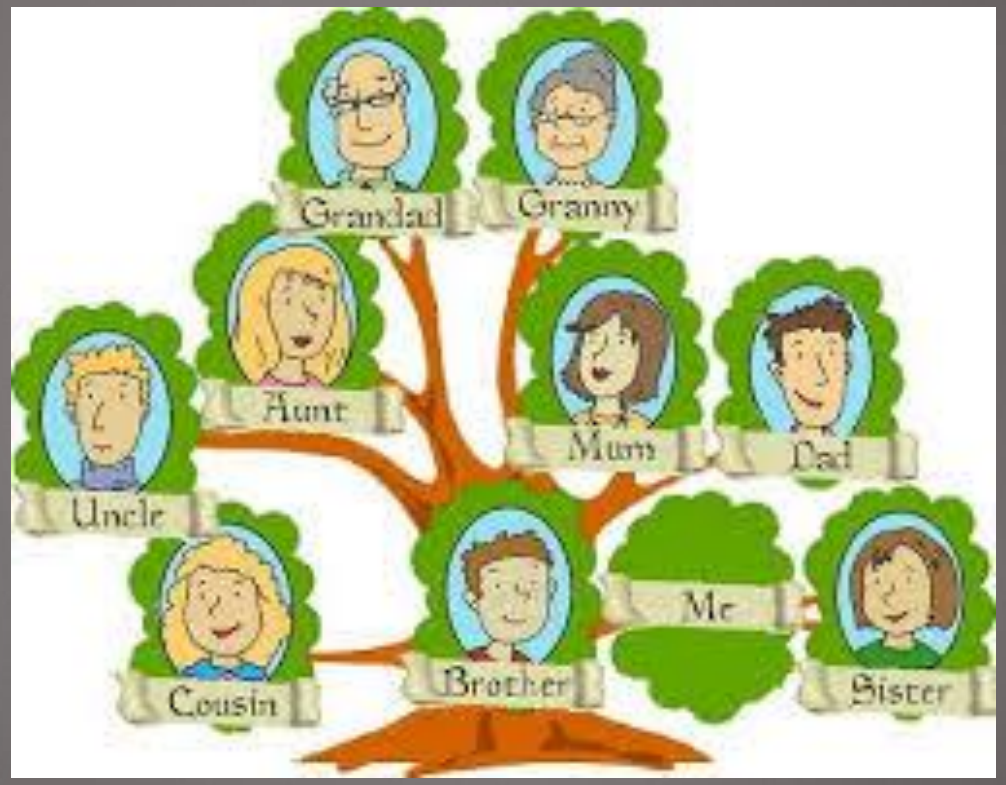
Sir William Osler

- *The Four Doctors* by John Singer Sargent, 1905, depicts the four physicians who founded Johns Hopkins Hospital. The original hangs in the William H. Welch Medical Library of Johns Hopkins University.
  From left to right: William Henry Welch, William Stewart Halsted, **William Osler**, Howard Kelly
- Founder John Hopkins Hospital
- Later Professor at Oxford
- Introduced clinical bedside training, residency and internship to medical training – '8 years of monastic life'!
- Many clinical signs and diseases named after him
- **Also first to notice hereditary nature of certain angioedema cases**

https://en.wikipedia.org/wiki/William_Osler

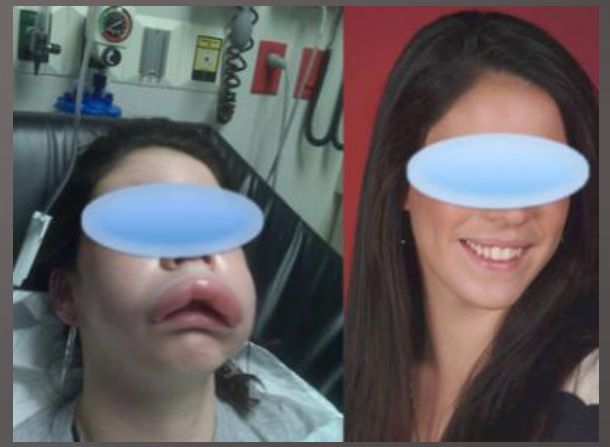

There are only two sorts of doctors:
those who practice with their brains,
and those who
practice
with their
tongues.
—William Osler
More science quotes at Today in Science History
todayinsci.com

Key questions – angioedema ?



Angioedema

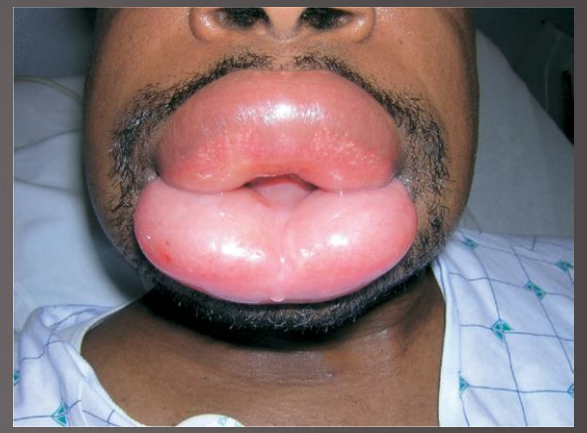
- Histaminergic/ mast cell mediated - acute setting in association with specific allergy or anaphylaxis
- Idiopathic (often in association with chronic urticaria) – may respond to antihistamines
- Non- allergic adverse drug reaction to Angiotensin Converting Enzyme (ACE) Inhibitors
- Hereditary – HAE Type 1, 2 and 3 – due to decreased level or function of C1 inhibitor enzyme
- Acquired C inhibitor deficiency

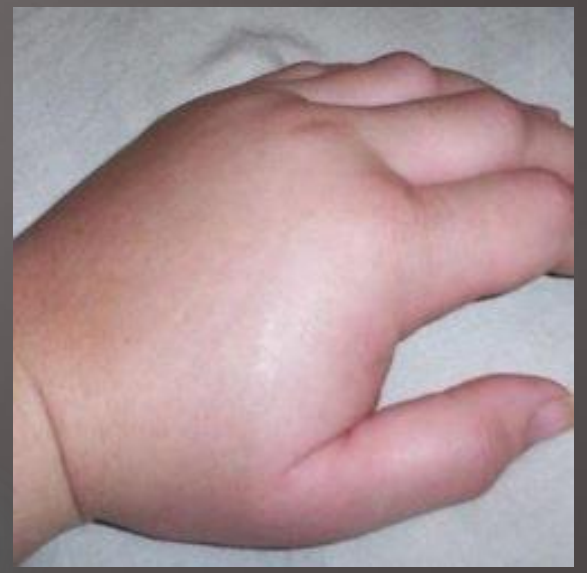


http://emedicine.medscape.com/article/135208-overview

Angioedema (non mast cell mediated)

- Asymmetric, nondependent swelling of deep tissues
- Painful rather than pruritic
- **Occurs without wheals**
- Bradykinin mediated swelling
- ACE- Inhibitors most common cause
- Differential includes hereditary angioedema (HAE), acquired C1-inhibitor deficiency and idiopathic angioedema





Practice parameter

A focused parameter update: Hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor–associated angioedema

Chief Editors: Bruce L. Zuraw, MD, Jonathan A. Bernstein, MD, and David M. Lang, MD

J Allergy Clin Immunol June 2013

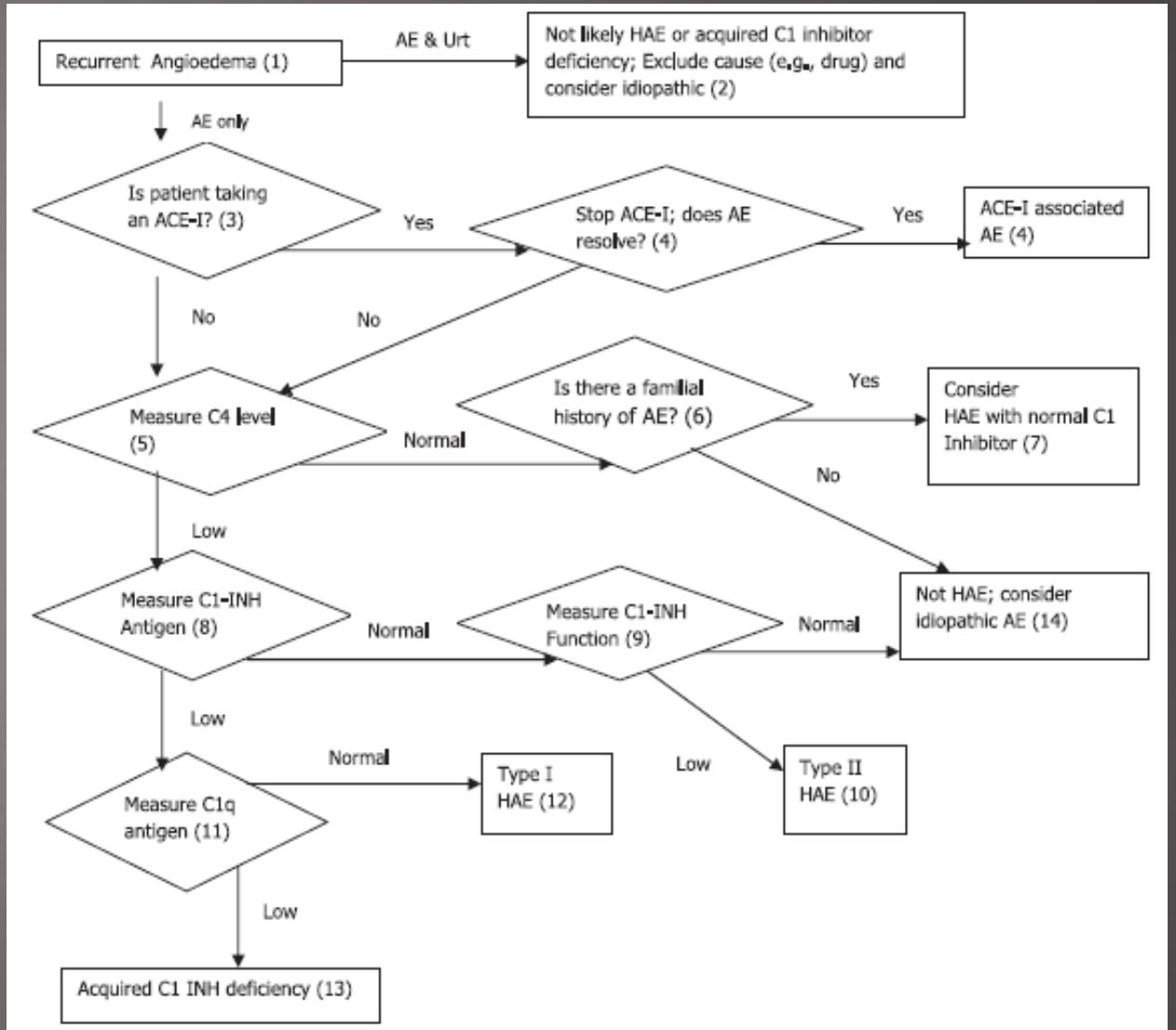
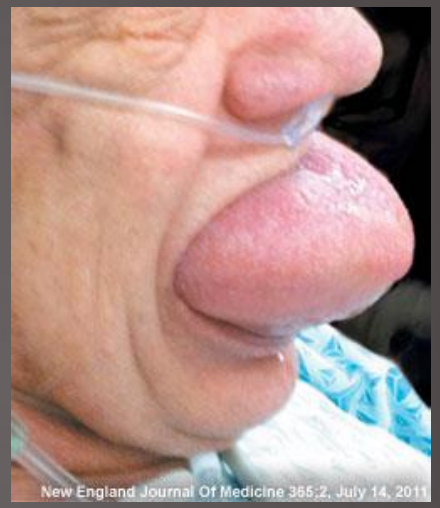


FIG E1. Recurrent angioedema diagnostic algorithm. *AE*, Angioedema; *URT*, urticaria.

Angioedema due to ACE-inhibitors

- Angiotensin Converting Enzyme – dipeptidyl carboxypeptidase important in breakdown of bradykinin
- **ACE-Inhibitors – inhibits the enzyme thereby prolonging breakdown of bradykinin, leading to angioedema**
- ACE-I associated with angioedema in 0.1 to 0.7% of patients
- COMMON due to wide use of these drugs (increasing chronic diseases of lifestyle, strong indications in diabetes, renal and cardiac conditions…)
- Class effect – not 'allergic'/ immune mediated
- Angiotensin Receptor Blockers (ARB's) less commonly associated, but also possible



Angioedema due to ACE-inhibitors

- Face and tongue frequently involved – AIRWAY NB during acute attacks!!!
- Can happen at any time, even after YEARS of treatment
- Class effect to all ACE-Inhibitors
- African patients are more at risk, also females, smokers and with increasing age
- Acute treatment controversial – AH's, adrenaline tried but not effective
- FFP, specific Rx for HAE has been tried, tracheostomy may be needed
- Management - discontinuation, Medic Alert, counselling

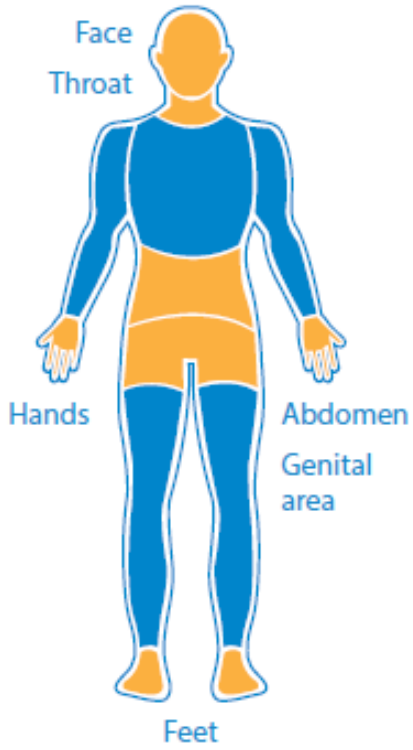
  " AVOID THE ACE of Spades"
- ARB's – modest risk of recurrence (only use with caution

  if benefits outweigh risks – C/I according to package inserts)

Hereditary angioedema

What is Hereditary Angioedema (HAE)?

HAE is a rare inherited condition characterized by painful, recurring attacks of swelling in parts of the body including:[1,2]



It is the result of a problem with a protein called C1 esterase inhibitor.

There are three types of hereditary angioedema:

Type I

- 85% of cases[3]
- C1-INH is decreased or not present[4]

Type II

- 15% of cases[3]
- C1-INH is not working properly[4]

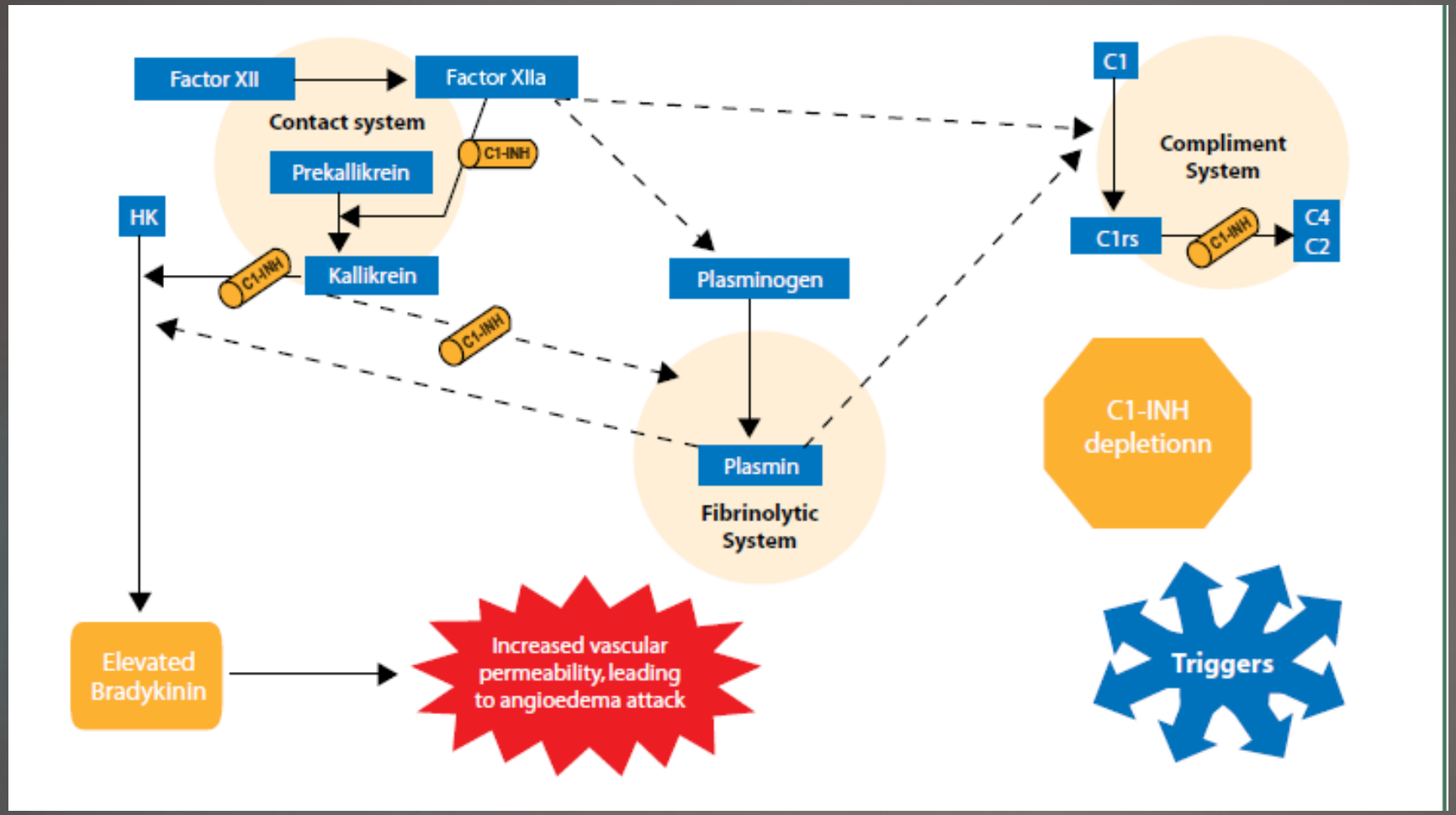
Type III

- Rare; prevalence is unknown[5]
- Diagnosed by genetic testing[6]

C1 inhibitor is important regulator of complement pathway

- Autosomal dominant condition
- Incidence + - 1:50 000
- ‘Runs in families’ – child of affected person has 50% chance of being affected
- New mutations can occur
- Type I, II – distinguished by C1 inhibitor levels, functional assays
- Type III – Poorly understood, mostly females – association with menstrual cycle, oestrogen levels

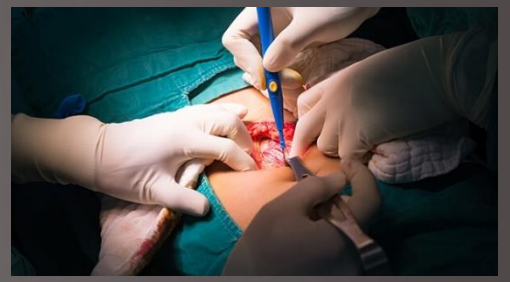
Hereditary angioedema - simplified pathophysiology

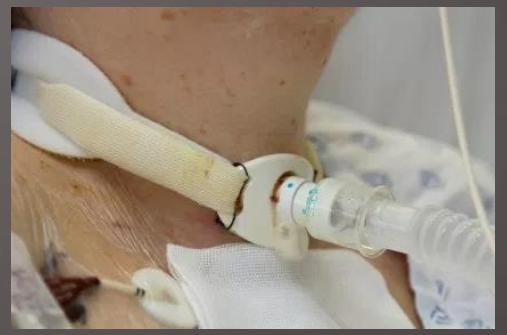


HAE results from mutations in gene encoding C1 inhibitor, a key plasma protease inhibitor involved at multiple points in the contact, fibrinolytic and complement systems. Normally C1 inhibitor prevents the cascades from becoming over active. In HAE, inadequate amount or ineffective C1 inhibitor can not regulate cascades and overproduction of bradykinin results.

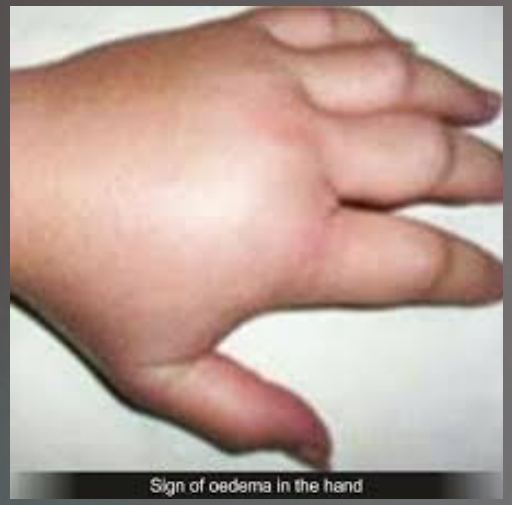
Clinical manifestations of HAE

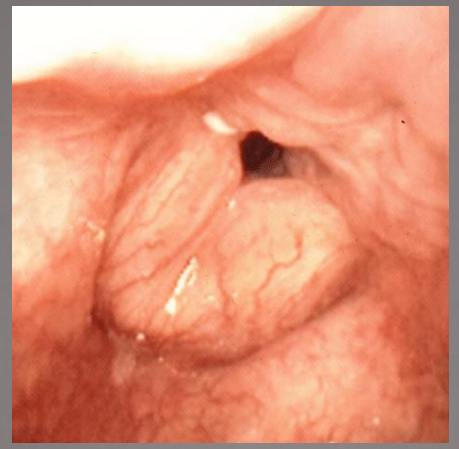
- Onset of symptoms often after puberty
- Attacks may be classified as peripheral, gastrointestinal or involving the airway
- Delay in diagnosis (often >8 years!) common
- Inappropriate treatment, especially for GI attacks
- Family history useful, but not always present
- Attacks may be triggered by surgery, trauma or stress
- Prodromal symptoms may include fatigue, irritability, nausea, rash – individual variation

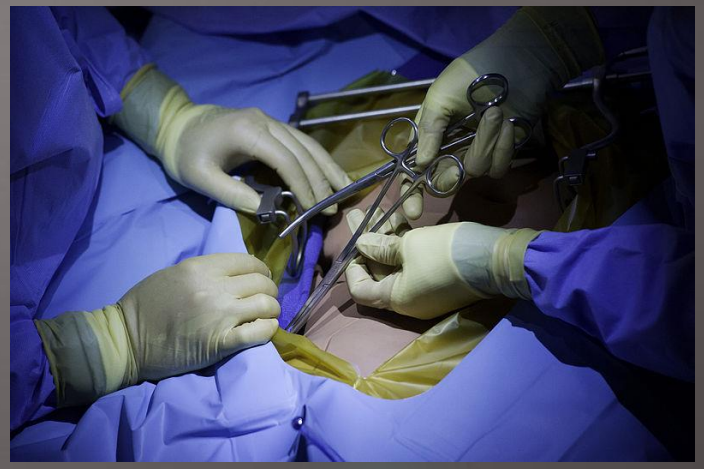




Clinical manifestations HAE

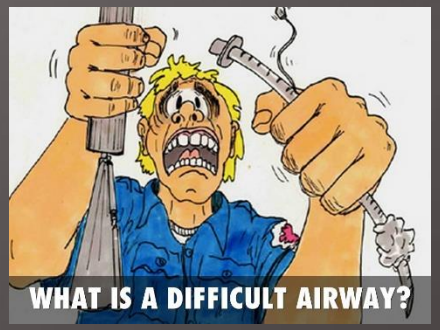




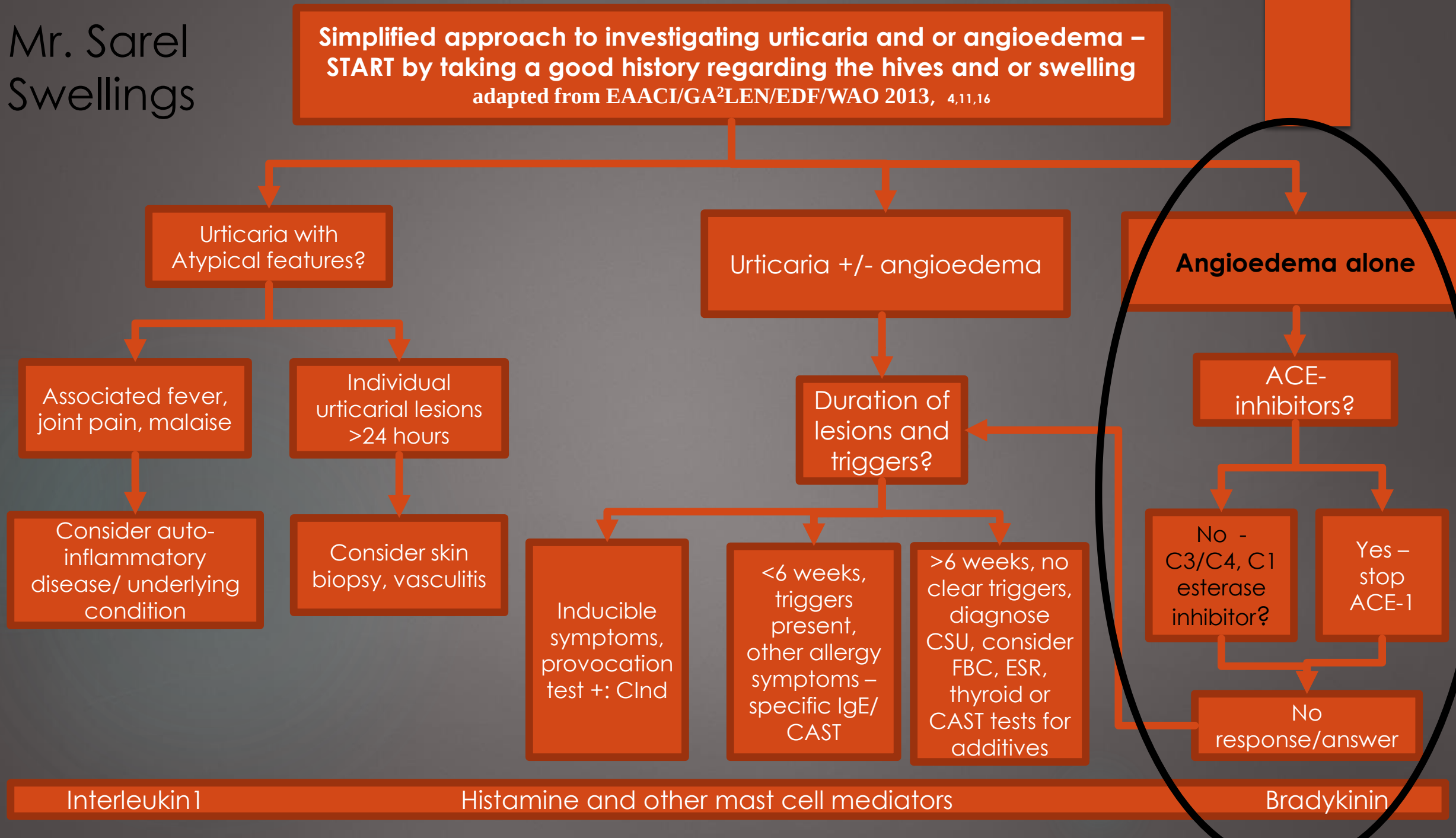


Case 4 – Sarel Swellings

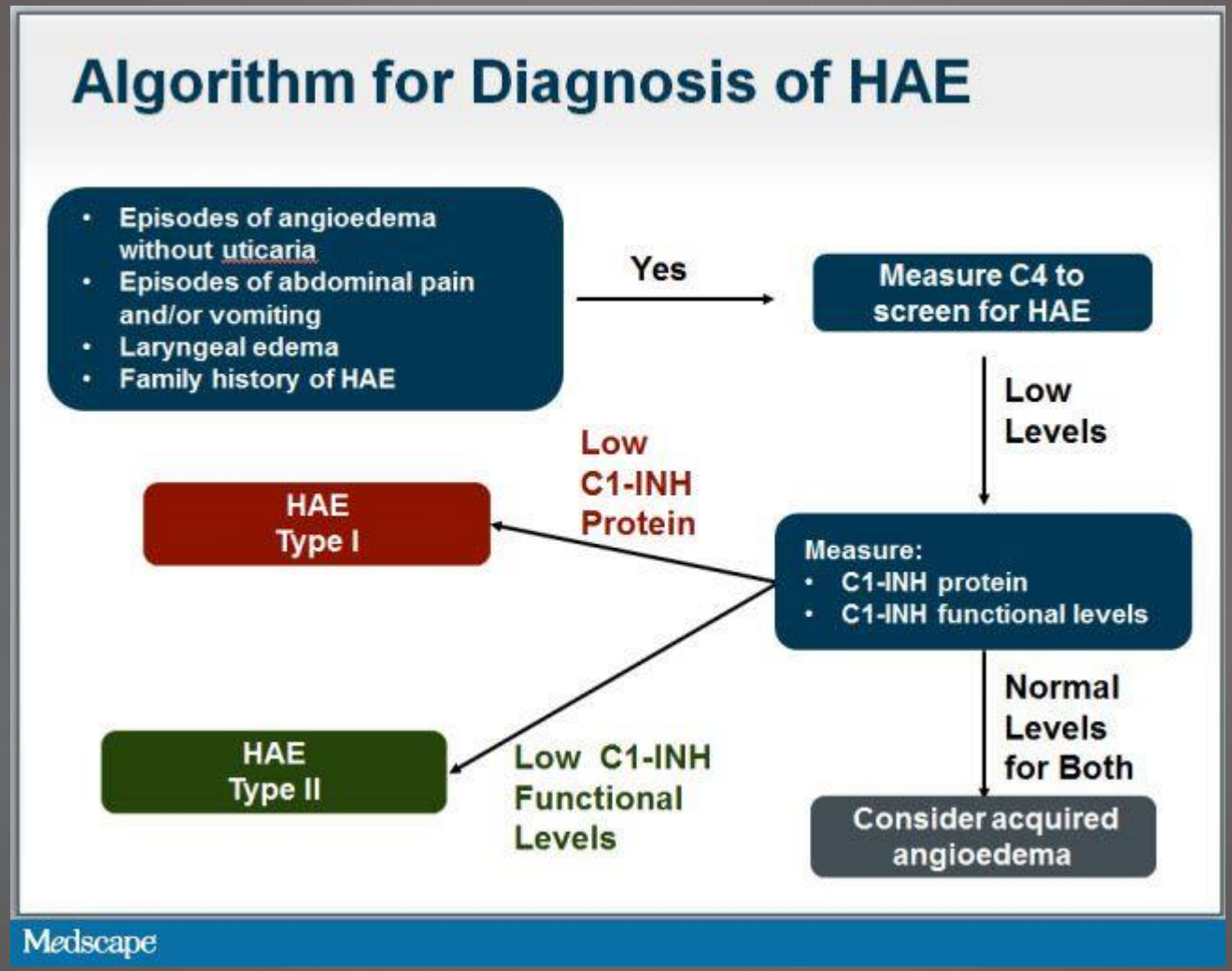
- 25 year old male
- History of spontaneous non pitting oedema of hands, feet and genital area since adolescence
- Painful, takes long to resolve
- Previous admission for intravenous fluids following severe abdominal cramps and vomiting, regarded as food poisoning
- Emergency room admission for angioedema of the face and airway



Mr. Sarel Swellings



Investigations for Hereditary Angioedema



How is a diagnosis of HAE confirmed?

Requires quantitation of C4 and quantitation of C1-INH by protein and function. A low C1q level (seen in ~70%) is associated with acquired C1-INH deficiency[9]

Laboratory Evaluation of Angioedema[9]

Type	C4[†]	C1-INH protein	C1-INH function[‡]	C1q[§]
Type I	↓	↓	↓	N
Type II	↓	N or ↓	↓	N
Type III	N	N	N	N
ACE inhibitor	N	N	N	N
Idiopathic	N	N	N	N
Acquired C1-INH deficiency	↓	↓	↓	↓

Adapted from Kaplan et al.

[†] Decreased in 95% of patients with type I and type II HAE.
[‡] Symptoms typically occur when functional activity is 35% or less.
[§] Decreased in approximately 70% of patients with acquired C1-INH deficiency. Markedly reduced in rare type I HAE patients with homozygous deficiency.
ACE = Angiotensin-converting enzyme
INH = Inhibitor
N = Normal

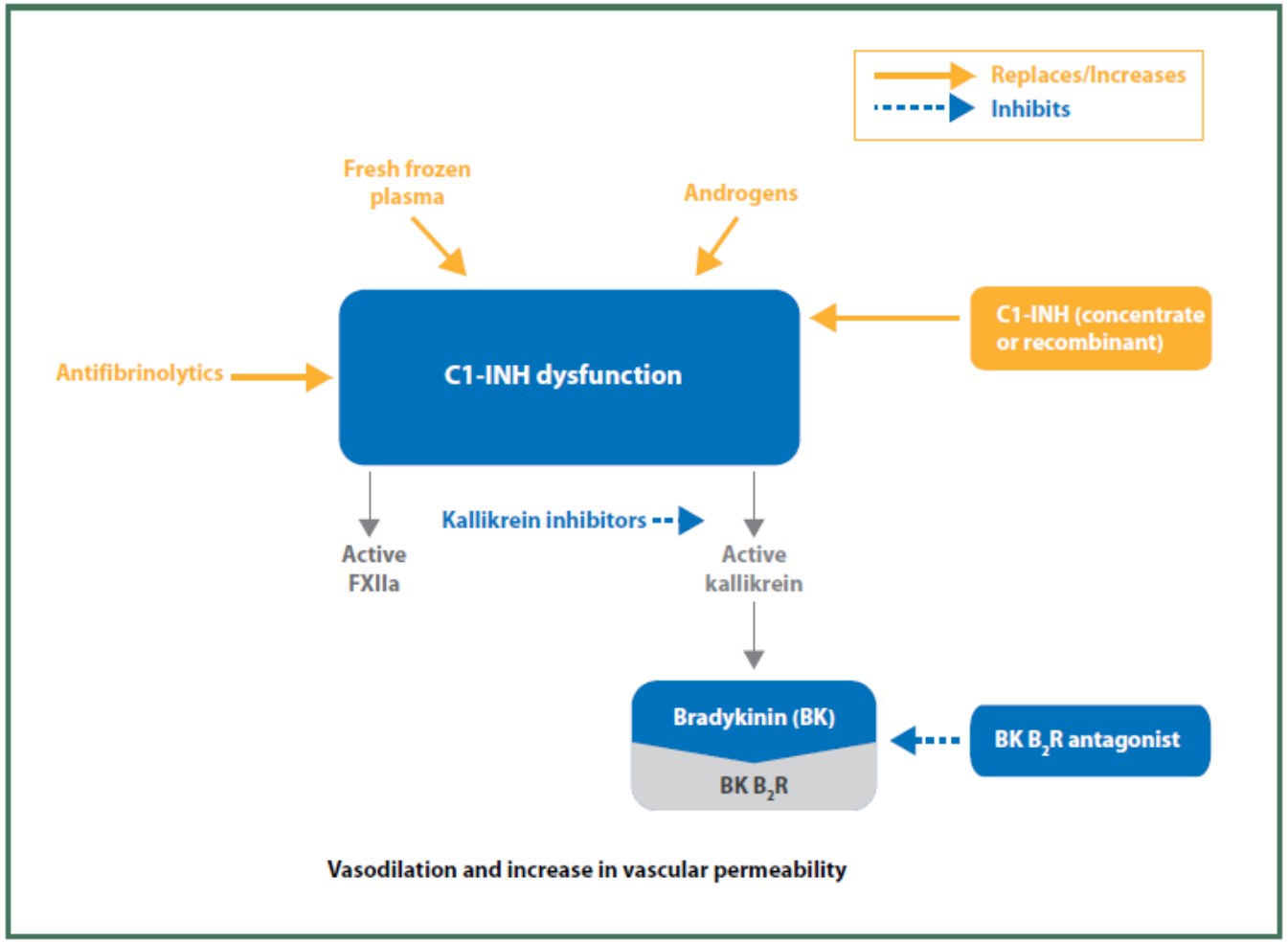
NB – Acquired C1 inhibitor deficiency may be associated with haematological conditions

Management of HAE

Can HAE be managed?

Optimal management of HAE includes treatment of acute attacks, short-term prophylaxis to prevent an attack, and long-term prophylaxis to minimize the frequency and severity of recurrent attacks.[3]

HAE targeted therapies include C1-esterase inhibitors, kallikrein inhibitors, and bradykinin receptor antagonists.[13]

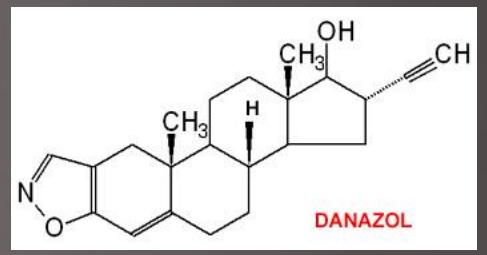


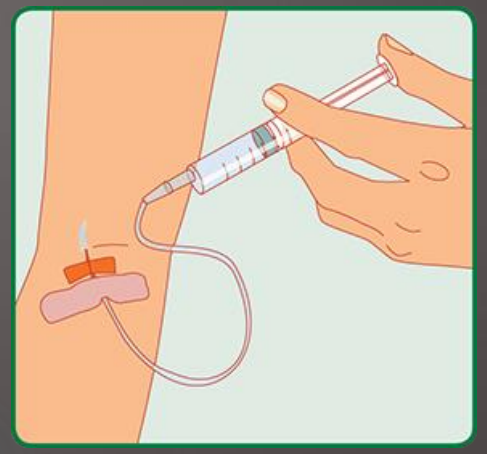
HAE treatment - Emergency

- No response to antihistamines
- Adrenaline – perhaps transient benefit
- Guard the airway and prepare for advanced airway if needed
- Specialist consultation/ management if available
- **C1 Inhibitor concentrate (human plasma derived)- if available**
- **Bradykinin receptor blockers (icatibant)**
- **Kallikrein inhibitors (ecallantide)**
- **Fresh Frozen Plasma contains C1 inhibitor – alternative**
- Avoid inappropriate surgical intervention for abdominal symptoms
- Treat nausea and vomiting, dehydration symptomatically

Management of HAE - Prophylaxis

- **Short term prophylaxis** – e.g. pre surgery or dental procedures – during time period or procedure likely to trigger an attack.
- Consider prophylactic administration of C1 inhibitor concentrate, FFP or high dose androgen (e.g. danazol)
- **Long term prophylaxis** – not needed in every case
- Avoid ACE inhibitors, known triggers, severe stress
- 17 alpha alkylated androgens (danozol) – low to medium dose relatively effective and safe, monitor BP and liver fx (NOT in pregnancy!)
- Fibrinolytics – somewhat effective, relatively safe
- Plasma derived C1 inhibitor concentrate (t1/2 >30 hours) – COST
- On demand Rx - patient can self inject



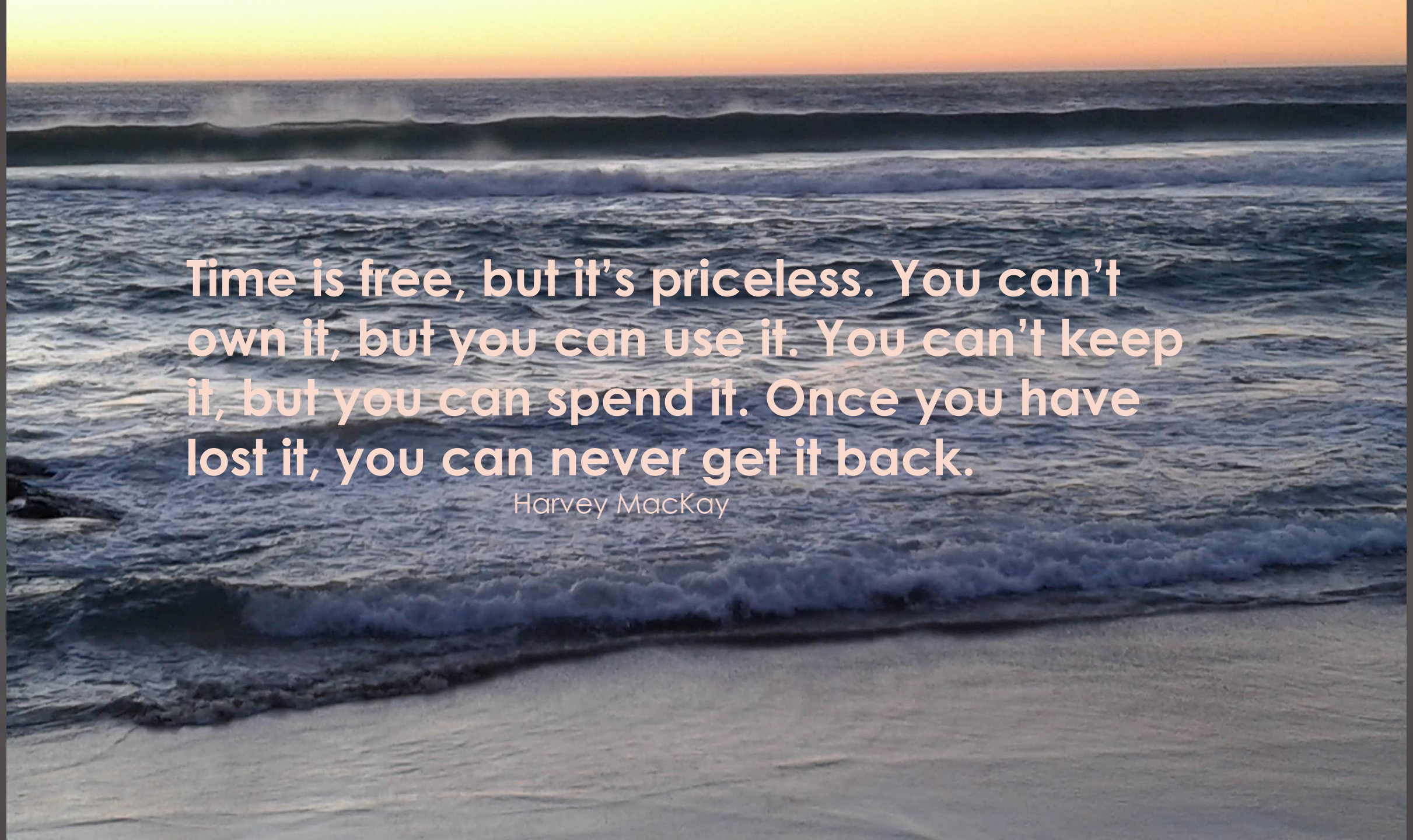


Case 4 – Sarel Swellings

- Decreased C4, decreased C1 inhibitor levels
- Diagnosed with Hereditary Angioedema Type 1
- Given an HAE identification card and advised to join Medic Alert
- Warned regarding possible triggers for acute attacks – surgical and dental procedures, trauma and stress
- Options discussed for treatment of acute attacks and prophylaxis - androgen (Danazol)
- Advised to have other family members screened

Conclusions - Angioedema

- Angioedema can be mediated by mast cells (histamine) or bradykinin
- Adverse reactions to angiotensin inhibitors (ACE-Inhibitors) common
- Hereditary angioedema may present with airway obstruction peripheral swelling , or gastrointestinal attacks
- Early identification is important – C4 as screening test and C1 inhibitor levels and function to confirm
- Acute attacks may not respond to antihistamines and adrenaline, may need airway management. Rx with plasma derived C1 inhibitor, FFP
- Prophylaxis to be considered – danazol or 'on demand' C1 inhibitor Rx
- Medic Alert, ID cards, support groups and screening of families.


Time is free, but it's priceless. You can't own it, but you can use it. You can't keep it, but you can spend it. Once you have lost it, you can never get it back.
Harvey MacKay

Thank you

- To the ALLSA committee for the invitation
- To the audience for travelling and making yourselves available to listen and learn!
- To past and current teachers and mentors in the field of Allergology
- To colleagues and team at the UCT Lung Institute
- To patients for sharing their stories and experience

Enjoy the rest of the conference!

References

- ALLSA Handbook of Practical Allergy, RJ Green, C Motala, PC Potter, 3rd Ed
- Omalizumab for chronic urticaria. J Allergy Clin Immunol Pract. 2016; 2 (1): 118-119
- HAE Canada www.haecaanada.org, accessed 10 Sep 2017, including Shire Canada information material
- Holtzhausen J. Urticaria and Angioedema – More than just Skin Deep! S Afr Fam Pract. 2017; 59(1): 32-36
- Kaplan A. Therapy of chronic urticaria: a simple, modern approach. Ann Allergy Asthma Immunol. 2014; 112: 419-425
- Khan S, Maitra A, Hissaria P. Chronic Urticaria: Indian Context – Challenges and Treatment Options. Dermatology Research and Practice, 2013
- Kim D H, Sung N H, Lee A Y. Effect of Levothyroxine Treatment on Clinical Symptoms in Hypothyroid Patients with Chronic Urticaria and Thyroid Autoimmunity. Ann Dermatol. 2016; 28 (2): 199-204
- Lunge S B, Borkar M, Pande S. Correlation of serum antithyroid microsomal antibody and autologous serum skin test in patients with chronic idiopathic urticaria. Indian Dermatol Online J. 2015; 6(4): 248–252
- Makris M P, Papadavid E, Zuberbier T. The use of biologicals in cutaneous allergies – present and future. Curr Opin Allergy Clin Immunology. 2014; 14: 409-416
- Maurer et Al – Chronic Urticaria, Challenges, Insights and New Directions, Proceedings of the second Global Urticaria Forum, Nov 2015, Berlin. (Published in JEADV, Volume 30 Supplement 5 July 2016)
- Medscape - http://emedicine.medscape.com/article/135208-overview, accessed 9 Sep 2017
- Zuberbier T, Aberer W, Asero R et al. The EAACI/GA2LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update Allergy 2014;69(7):868–87.
- Zurow B L. A Focused Parameter Update, Hereditary Angioedema, Acquired C1 inhibitor deficiency and ACE-Inhibitor associated angioedema J Allergy Clin Immunol June 2013